DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Charles J. Coté, M.D.
Massachusetts General Hospital
Department of Anesthesia and Critical Care
55 Fruit Street
Boston, MA 02114

Ref: 09-HFD-45-02-04

Dear Dr. Coté:

Between April 14 and 30, 2008, Ms. M. Patricia Murphy and Ms. Michelle M. Noe, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drug Zemuron® (rocuronium bromide), performed for Organon:

- Protocol (b) (4) entitled, "An open-label, randomized, phase IIIB, multicenter trial to evaluate the pharmacodynamic parameters of intubation bolus, and bolus and infusion maintenance doses of Zemuron® in pediatric and adolescent subjects" and
- Protocol (b) (4) entitled, "A randomized, assessor-blind, dose-ranging, phase IIIB, multicenter trial comparing the intubating conditions and time course of block of three different intubating doses (0.45 mg/kg, 0.6 mg/kg and 1.0 mg/kg) of Zemuron® in pediatric and adolescent subjects under general anesthesia."

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your May 22, 2008 written response to the Form FDA 483, Inspectional Observations, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Murphy and Ms. Noe presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to conduct the studies according to the signed investigator statement [21 CFR 312.60].**

   When you signed the investigator statements (Form FDA 1572) for the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator. You specifically agreed to personally conduct, or supervise those aspects of the study you did not personally conduct, and to ensure that all associates, colleagues, and employees assisting in the conduct of the study were informed about their obligations.

   a. You failed to adequately supervise individuals to whom you delegated study tasks. The FDA inspection revealed that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trials were conducted according to the signed investigator statement and applicable regulations. Your failure to provide adequate oversight resulted in inadequate informed consent documentation and inadequate and inaccurate records as outlined in items 2 and 3 below. In your May 22, 2008 response to the Form FDA 483, you stated that although you were personally involved in the study, you did not ensure that the delegated staff were fully trained, and you did not verify their performance as documented in the case report forms (CRFs). We acknowledge your assurance that corrective actions have been taken to assure more rigorous documentation.

   b. Regarding protocol (b) (4), you did not list the names of all subinvestigators who would be assisting in the conduct of the investigation, as required by the Statement of Investigator, Form FDA 1572. The FDA regulations specified that in the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team [21 CFR 312.3(b)]. During the inspection, you told the FDA investigator that the protocol-required blinded assessments were done by residents present in the operating room on the day of surgery. By performing these significant study activities, the residents should have been listed on the Form FDA 1572 as subinvestigators. We acknowledge your assurance that in the future, the individuals who are involved in research-related assessments will be included on a Form FDA 1572.

2. **You failed to obtain legally effective informed consent [21 CFR part 50 and 21 CFR 312.60].**

   Except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative [21 CFR 50.20]. Informed consent must be documented by the use of a written consent form approved by the institutional review board (IRB) and signed and dated by the subject or the

subject's legally authorized representative at the time of consent [21 CFR 50.27(a)]. You also failed to obtain proper assent as determined to be appropriate by the IRB [21 CFR § 50.55].

a. Fabricated signatures of the subject's legally authorized representative were found on the consent forms for subjects 114403 and 114601, who were enrolled in protocol (b) (4), and subject 124402, who was enrolled in protocol (b) (4). We note that you discovered the fabricated signatures through your own internal audit, and that you sent letters dated September 10, 2007 to the parents of subjects 114403 and 114601, and a letter dated December 11, 2007 to the representatives of subject 124402, requesting that the informed consent documents be signed again. In addition, you promptly reported the findings to the IRB. In your May 22, 2008 response to the Form FDA 483, you stated that you asked the study coordinator to ensure that copies of the original, signed consent forms were placed in the subjects' medical records, according to institutional policy, but you did not confirm this action. You stated that had this occurred, you would have been able to retrieve a copy of the original consent forms. You stated that it is presumed that your former research nurse (study coordinator) apparently falsified the signatures after she lost the original, signed consent forms. You also stated that you reported these findings to the Board of Registration in Nursing. As the clinical investigator, you are responsible for oversight of study activities delegated to study staff.

   In your written response you also stated that you took immediate action to contact the families that had consent forms with apparently false signatures. You stated that you was able to reach two out of three and they sent confirmatory signed statement that they had allowed their child to participate in a research project prior to study procedure. You stated that the third family had vacated their apartment and you were not able to contact them. You stated that documentation by the CRO exists to confirm that you did in fact obtain consent from all subject parents prior to participation in the study on a valid consent form. We do not find your response to this observation adequate as it does not include documentation to support your statements.

b. Regarding protocol (b) (4), page 5 of the informed consent document asks "Do you agree to allow your child to have blood samples taken?" followed by a space for the subject or subject's legally authorized representative to respond by checking "YES" or "NO" and initial. However, pharmacokinetic samples were collected from subjects without obtaining informed consent for blood sampling. Examples include, but are not limited to, subjects 114403 and 114503. We note that you sent a letter dated December 11, 2007 to the IRB informing the IRB that these subjects did not consent to blood draw. In your May 22, 2008 response to the Form FDA 483, you stated that you will ensure that you are aware of any options sections included in the body of the consent form. However, you did not state how you will ensure that proper consent is obtained.

c. Regarding protocol (b) (4), the IRB requires that subjects who are 7-13 years old sign a Research Assent form. Subject 124501 was seven years old at the time of

consent, but did not sign a Research Assent form prior to being enrolled in the study. We note that you sent the subject's representative a letter dated December 11, 2007 requesting that the subject sign and date a Research Assent form. Therefore, you failed to obtain proper assent as determined to be appropriate by the IRB [21 CFR § 50.55].

d. According to the study records, representatives for subjects 114302 and 114504 were non-English speaking. The subjects' representatives signed informed consent documents written in English rather than a language understandable to the representatives. The subjects' representatives were not provided with either a translated consent document or a "short form" translated consent document. We note that the names of the translators were written on the signed consent documents. In your response to the Form FDA 483, you acknowledged that you failed to provide translated consent documents to these subjects, but stated that you would train your staff on this requirement so it would not happen in the future. We acknowledge your assurance that corrective actions will be taken to ensure that this finding is not repeated in any future studies.

e. Informed consent documents were dated by study personnel rather than the legally authorized representative for subjects 114302, 114401, and 114504 enrolled in protocol (b) (4), and subject 124601 enrolled in protocol (b) (4). In your May 22, 2008 response to the Form FDA 483, you acknowledged that it was your routine practice to insert the date yourself, prior to the parents' signatures, in order to simplify the process. You stated that you now know that subjects and parents must date the consent forms themselves. We acknowledge your assurance that corrective actions have been taken to ensure that this finding is not repeated in any future studies.

3. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

Examples include, but are not limited to, the following:

a. Regarding protocol (b) (4) the primary efficacy parameter was the total dose from administration of intubating dose to reappearance of T_3 after the last maintenance bolus dose of Zemuron®, or discontinuation of Zemuron® infusion. The duration of drug administrations used to calculate the total dose (mg) does not correspond to the time interval of drug administration recorded on the Train-of Four Watch (TOF-Watch) source document for the following subjects:

Subject No.	TOF-Watch (mcg/kg/min)	TOF-Watch Source Document Time (h:mm:ss) / Duration (mm:ss)	Duration Used in Calculation
114403	adjust to 14 adjust to 12 adjust to 8	10:15:49-10:23:28 / 7:39 (**459 sec**) 10:23:28-10:28:18 / 4:50 (**290 sec**) 10:31:57-10:44:58 / 13:01 (**781 sec**)	**499 sec** **429 sec** **790 sec**
114404	start at 10 adjust to 12 adjust to 10 adjust to 8 adjust to 6 adjust to 4 adjust to 2 adjust to 5 adjust to 4 adjust to 6	13:36:52-13:39:09 / 2:17 (**137 sec**) 13:39:09-13:42:01 / 2:52 (**172 sec**) 13:42:01-13:44:25 / 2:24 (**144 sec**) 13:44:25-13:47:52 / 3:27 (**207 sec**) 13:47:52-13:51:02 / 3:10 (**190 sec**) 13:51:02-13:54:38 / 3:36 (**216 sec**) 13:54:38-14:03:33 / 8:55 (**535 sec**) 14:03:33-14:15:01 / 11:28 (**688 sec**) 14:23:24-14:46:14 / 22:50 (**1370 sec**) 14:46:14-15:15:39 / 29:25 (**1765 sec**)	**177 sec** **212 sec** **165 sec** **186 sec** **230 sec** **226 sec** **565 sec** **128 sec** **1402 sec** **1773 sec**
114501	start at 10	14:42:40-14:48:07 / 5:27 (**327 sec**)	**361 sec**
114505	adjust to 8 adjust to 5 adjust to 5	9:01:32-9:6:10 / 4:38 (**278 sec**) 9:26:45-9:37:25 / 10:40 (**640 sec**) 9:55:54-10:07:15 / 11:21 (**681 sec**)	**318 sec** **680 sec** **721 sec**
114602	start at 10 adjust to 8	12:56:21-13:04:20 / 7:59 (**479 sec**) 13:09:52-15:25:32 / 2:15:40 (**8140 sec**)	**519 sec** **8732 sec**
114603	adjust to 8 adjust to 2	12:34:59-12:38:29 / 3:30 (**210 sec**) 12:41:52-13:00:45 / 18:53 (**1133 sec**)	**220 sec** **1128 sec**
114607	adjust to 5	11:43:04-12:00:49 / 17:45 (**1065 sec**)	**1125 sec**

b. Regarding protocol (b) (4), the "Infusion Rate (mL/min)" was not recorded for the 10 subjects who were randomized and received the infusion maintenance dose for protocol (b) (4). In your May 22, 2008 response to the Form FDA 483, you acknowledged you recorded the dose in mcg/kg/min that was obtained from the computer generated TOF-Watch and did not appropriately calculate the infusion rate in ml/min.

c. The study records indicate that informed consent for subject 114403 enrolled in protocol (b) (4) was obtained on June 2, 2006, and informed consent for subject 124402 enrolled in protocol (b) (4) was obtained on November 30, 2006. Each of these informed consent documents contains a signature similar to yours entered on the line above the statement “Study Doctor or Person Obtaining Consent.” During the inspection, you stated that the signatures on these documents were not yours. In your May 22, 2008 response to the Form FDA 483, you stated that the signatures on these documents were fabricated.

d. Regarding protocol (b) (4) the "Concentration of Zemuron® Infusion (mg/mL)" on the source document for the administration of (infusion) maintenance dose was recorded as "1:1" or "0.5:1" for subjects 114201, 114406, 114505, 114602, 114603 and 114607. Based on this documentation, the actual drug concentration is uncertain. In addition, the concentration on the source document does not match the concentration reported on the CRF for subject 114501. In your response to the FDA Form 483, you stated that your research nurse recorded these doses. You also stated that, in the future, you will ensure that staff delegated to document specific information, such as dilutions, are adequately trained on how to do so.

We acknowledge your assurance that corrective actions have been taken to ensure that the findings in item 3 are not repeated in any future studies.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leslie Ball

3/2/2009 06:17:05 PM